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THE EFFECT OF AGING ON PHENYLEPHRINE RESPONSE IN NORMAL SUBJECTS

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ABSTRACT

INTRODUCTION: With aging, cardiac responses to β-adrenergic stimulation decline but the responses to α_1-stimulation are less clear. Moreover, whether aging, in the absence of disease, influences the left ventricular response to an increase in afterload is unclear. This study examined the effect of aging on heart rate (HR), blood pressure (BP), cardiac index (CI) and several left ventricular contractility measurements during α_1-stimulation with a phenylephrine infusion. *METHODS:* Subjects were rigorously screened to be normal by history, physical, blood tests, ECG, ETT and echocardiogram. Twelve young (mean 26 years, all male) and 15 aged (69 years, 11 males) subjects were studied during 10 minute infusions of phenylephrine at 0.5 and 1.0 mcg/kg/min. HR, BP and radionuclide ventriculographic cardiac volumes were measured. *RESULTS:* Systolic BP increased more in the aged than in the young (22 vs. 13%, p=0.003), while heart rate (16 vs. 21%, p=0.05) fell less. Contractile responses to phenylephrine , including EF, stroke volume index (SVI), stroke work index and left ventricular contractility index were not altered with aging. Systemic vascular resistance (SVR) was higher at baseline and at each infusion rate, but there was no age-associate change in the response to PE. *CONCLUSIONS:* In a healthy normal aged population, a preserved SVI response in the setting of a higher baseline SVR results in an increased SBP response to α_1-stimulation. Contractile responses to increased afterload are not altered with aging. Age-associated differences in the response to α_1-stimulation are small and are explained by altered baroreflex sensitivity and a stiffer vasculature.

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INTRODUCTION

Autonomic regulation of cardiovascular function changes with aging. For example, human and animal studies have consistently shown a decrease in beta adrenergic responsiveness with aging, with reduced heart rate, ejection fraction, blood pressure and cardiac output responses to beta adrenergic stimulation with isoproterenol. In addition, there is abundant evidence of reduced cardiac vagal tone with aging as manifested by reduced heart rate variability. Whether alpha adrenergic responsiveness alters with aging is less clear. *In vitro* animal studies have shown both an increased[1], reduced[2,3] or unchanged[4] α_1-mediated phenylephrine response. *In vitro* human studies have shown an increased[5] or reduced[6] α_1-mediated phenylephrine response in isolated artery preparations. *In vivo* examination of the vascular response to α_1-stimulation has been found to be reduced with age in the rat hindlimb[7] but unchanged by aging in the beagle hindlimb[8]. Human *in vivo* studies have shown an age-associated reduction in α_1-mediated phenylephrine response in forearm blood flow[9] but an overall increase in the blood pressure response to phenylephrine with increasing age[10]. Thus, the effect of aging on the cardiovascular response to α_1-stimulation varies with the portion of the vascular bed examined. In addition, conflicting results in prior human studies may also be due to the rigor with which confounding diseases such as hypertension are excluded.

Alpha receptors are of two types. The majority of myocardial alpha receptors are of the α_1 subtype[11]; α_1 receptors mediate smooth muscle constriction, arterial vasoconstriction, and cause a positive inotropic effect. Alpha 2 receptors mediate inhibition of sympathetic neurotransmission in the heart by inhibiting norepinephrine release at the presynaptic level.

Although most studies at rest have shown no age-associated reduction in ejection fraction with aging[12,13], some have postulated that this can be "uncovered" by maneuvers that increase afterload, such as mental stress[14] or phenylephrine infusion[15]. Phenylphrine is an α_1 selective agonist and causes at least some inotropic effect but also causes vasoconstriction leading to an increase in blood pressure and afterload. Unfortunately these prior investigations showing an age-associated change in contractility have been limited by the use of echocardiographically-derived measures of cardiac contractility[15], confounded by drugs used to block the arterial baroreceptors[15], and had insufficiently rigorous methods of screening for confounding cardiac disease[14].

The purposes of this study were to determine whether α_1 responses are altered with aging and whether the contractile response to an increased afterload declines with aging. We hypothesized that the older adult population will demonstrate an increased systolic blood pressure (SBP) response to phenylephrine and that the use of more reproducible radionuclide angiographic measures will demonstrate preserved contractile responses to an increase in afterload in older subjects.

METHODS

Subjects

The subjects studied consisted of 12 young (aged 22 to 33) and 18 older (aged 63 to 80) healthy adults. All 12 of the younger subjects and 11 of the older subjects were male. Subjects were excluded if they had any history of angina, myocardial infarction, stroke, hypertension, chronic pulmonary disease, diabetes, current medication use (prescription or over the counter), current smoking, or exercise-limiting orthopedic impairment. Entry requirements included a normal blood pressure, a normal physical exam, normal resting ECG, normal M-mode and two-dimensional echocardiograms showing no more than mild valvular regurgitation, a normal Bruce protocol maximal exercise treadmill stress test, and a normal hematocrit, fasting blood glucose, total cholesterol, and creatinine. Two older subjects were excluded on the basis of this screening and an additional older subject was excluded secondary to problems with line placement. Therefore a total of 12 young subjects and 15 older subjects received phenylephrine infusion.

This study was approved by the Human Subjects Committee of the University of Washington, and all subjects gave informed consent.

Study Protocol

Intravenous catheters were inserted into a right hand vein and a right antecubital vein of each subject, after which they rested supine for 30 minutes before collection of baseline data. All studies were performed with the subject supine, and all were performed at the same time of day (10 AM to 12 noon). After the collection of baseline data, serial infusions of phenylephrine at 0.5 and 1.0 mcg/kg/min were given for 10 minutes each with a Medfusion 2010 infusion pump. The infusion solution was prepared by diluting a sufficient amount of phenylephrine in 0.5N saline to achieve a total injectate volume of 20 mL at each infusion level. Phenylephrine infusions were halted if the diastolic blood pressure (DBP) became greater than 100 mm Hg or if the systolic blood pressure (SBP) became greater than 200 mm Hg. No complications occurred, and all younger subjects received all two doses. One older subject did not receive the 1.0 mcg/kg/min phenylephrine dose since her blood pressure increased to 210/102.

Data Collection and Processing:

At rest and during the final 2 minutes of each infusion dose, cardiac blood pool images, heart rate, and blood pressure (using Ohmeda 2300 Finapres) were recorded. For radionuclide angiography, blood was obtained at the time of intravenous catheter placement and labeled with 20-30 mCi of ^{99m}Tc as previously described[16]. Images were acquired in the left anterior oblique projection, which offered the best septal definition, with a high-sensitivity parallel hole collimator and a General Electric 300 small-field-of-view camera interfaced to a Microdelta imaging terminal. Radionuclide images were acquired in 20-msec frames by forward and backward reconstruction with ±20% arrhythmia rejection; a single beat was dropped after each rejected beat[16]. Ejection fraction, end-diastolic volume index, and end-systolic volume index were calculated by previously described methods[16]. Cardiac index was obtained by multiplying the stoke volume index times the mean heart rate during the acquisition.

Derived Measurements

Mean arterial pressure (MAP) was calculated as [SBP + 2XDBP]/3. Total systemic vascular resistance (SVR) was calculated as MAP x 80 / CO. Stroke work index (SWI) was calculated as stroke volume index (SVI) X SBP; rate pressure product (RPP) as SBP X HR; left ventricular contractility index (LVCI) as SBP/ESVI. Effective E_a, an estimate of afterload that takes into account pulsatile flow was calculated as [2XSBP+DBP]/ 3 X SV. Root mean square difference (RMS Diff), which is calculated by taking the root mean square of the difference of successive RR-intervals, is a measure of heart rate variability used as a marker for vagal tone. Baroreceptor sensitivity (BRS) was calculated by performing a linear regression of the relationship between RR interval and SBP during the phenylephrine infusion[14,17,18].

Statistical Analysis

Results are expressed as the mean ± standard error. The results in all young and older subjects were compared by ANOVA for repeated measures. The reported probability values are those for phenylephrine effect, overall young/old effect and the interaction term (old versus young times dose). A value of $p \leq 0.05$ was considered significant.

Table 1—Subject Characteristics

Mean ± SEM	Young (n=12)	Older (n=15)
Age (years)	26.1±1.0	69.4±1.3*
Weight (kg)	81.8±6.1	75.1±2.6
Height (cm)	183±3	170±8*
Body Surface Area (m^2)	1.85±0.19	1.86±0.04
Body Mass Index (kg/m^2)	21.6±4.1	26.2±1.1

The symbol * designates a significant difference ($p<0.05$) between age groups.

RESULTS

Study Group Characteristics and Baseline Measurements:

Subject characteristics are summarized in Table 1. There was no difference between the two groups in terms of weight, body surface area, and body mass index.

Blood Pressure and Heart Rate Changes in Response to Phenylephrine

There was a significant increase in SBP ($p<0.0001$) and DBP ($p<0.0001$) with phenylephrine. The increase in SBP was significantly greater in the older as opposed to the younger group (22 versus 13%, $p=0.003$) as shown in Figure 2. The change in DBP in response to phenylephrine was not different between groups. There was also a significant drop in HR ($p=0.0001$) in response to phenylephrine, with the older group having a significantly lesser fall in HR as compared to the younger group ($p=0.05$).

The calculated baroreceptor sensitivity was significantly less ($p=0.02$) in the older group (7.49 ± 1.14 ms/mmHg) compared to the younger group (13.1 ± 1.84 ms/mmHg). The lower BRS was due to both a greater increase in SBP in the older group and a greater decrease in HR in the younger group.

Cardiac Volumes and Outputs:

Phenylephrine caused a significant increase in EDVI ($p=0.0001$) and ESVI ($p<0.0001$) which was not significantly different between the two groups. There was no significant effect of phenylephrine or group on SVI. Phenylephrine resulted in a significant decrease in CI ($p=0.003$), which was greater in the young than the older subjects (–0.50 vs. -0.09 L/min/m^2, $p=0.03$). The fall in cardiac index was due entirely to a decrease in the heart rate since SVI was unchanged in both groups.

Contractile Measures:

EF fell significantly in response to phenylephrine ($p<0.0001$) but the fall was not different between older and young subjects ($p=0.31$). Both the LVCI ($p=0.004$) and the SWI ($p<0.001$) showed a significant increase in response to phenylephrine. The increase in SWI in the older group was non-significantly greater than in the young ($p=0.07$), while there was no difference in the LVCI between groups ($p=0.39$).

SVR was significantly higher at rest and at all levels of phenylephrine infusion in the older as opposed to the younger group ($p=0.001$). As Figure 4 demonstrates, there was a significant SVR response to phenylephrine in the two groups ($p<0.0001$) but this response was not significantly different between the two groups. Vascular load or effective E_a was significantly higher in the older as opposed to the younger group ($p=0.0012$) but the phenylephrine response was not different between the two groups ($p=0.48$). PP/SVI (an estimate of vascular stiffness) was elevated in the older group ($p=0.005$) and there was a trend for a greater increase with phenylephrine in the older group ($p=0.06$). The RPP showed no significant change with phenylephrine infusion in either group.

Measures of Vagal Tone:

The RMS Difference between successive RR intervals was used as a measure of vagal tone in both groups. The older group had a significantly lower RMS Difference than the younger group ($p=0.02$). As shown in Table 3, there was a significant increase in RMS Difference with phenylephrine (consistent with augmentation of vagal tone) but this effect was not significantly different between the two groups ($p=0.62$).

Gender Differences

There were too few female subjects to be able to comment on gender differences in the phenylephrine response. All results, however, were unchanged when the female subjects were excluded from the analysis.

DISCUSSION

This study found an increase in the systolic blood pressure response to α_1 stimulation in the older group as compared to the younger group, but no age-associated reduction in left ventricular contractility in these rigorously screened older subjects. Older subjects had similar EF, SVI, ESVI, E_a, and LVCI responses to phenylephrine as younger subjects. Older subjects had a lesser decline in CI to phenylephrine due entirely to their lesser fall in heart rate, since stroke volume responses were not decreased with aging. The lesser heart rate decline in the older group appeared due to an impaired baroreceptor-mediated bradycardic response.

The SBP response to phenylephrine was greater in older subjects compared to the young (+29 mmHg old vs. +16 mmHg young). There are conflicting reports with regards to the effect of age on pressor responsiveness to phenylephrine. One small study ($n=6$ per group) that failed to rigorously screen subjects showed reduced responsiveness with aging[19], but two larger studies showed an increased blood pressure response with age, as we also demonstrated[10,20].

Jones et al. found a reduction in the systolic blood pressure response to acute α_1-stimulation in older male subjects[21] during ganglionic blockade with trimethaphan (in an attempt to control for the confounding effect of differences in vagal tone and response between young and older subjects). Unfortunately, trimethaphan has also been found to act secondarily as a direct arterial vasodilator as well as an α-adrenoceptor antagonist[22]. Given that trimethaphan's pharmokinetics are characterized by poor lipid solubility, the reduction in lean body mass seen with aging would result in older subjects receiving a higher effective dose of trimethaphan than the younger subjects. Perhaps the age-associated reduction in the BP response to phenylephrine seen by Jones et al. was in fact due to direct vasodilator and α-blockade in the older subjects.

What are the potential mechanisms for an increase SBP responsiveness to α_1-stimulation with aging? One possibility is an increase in α_1 sensitivity with aging. The results of this study do not support this theory because while SVR, E_a and PP/SVI were significantly elevated in the older group at rest, there was no statistically significant effect of age on the response of these measures to phenylephrine. If older subjects really did have an increased α_1 response, one would expect a greater increase in SVR, E_a and PP/SVI with acute administration of phenylephrine. It has been suggested previously in human studies that there is an age-associated decline in the α_1-mediated response in terms of forearm blood flow[9], while the results of *in vitro* animal artery preparations vary depending upon the technique and the location of the arterial preparation used. Further complicating this issue is the fact that there exist several α_1 receptor subtypes, which change their distribution with increasing age[23]. We did not examine arterial flow in this study, but we did determine an overall increased SBP response to α_1-receptor stimulation. The most likely explanation for the age difference in SBP response, as opposed to a direct change in receptor responsiveness, is the fact that the elderly subjects had a similar increase in SVI as the younger subjects. In the setting of a stiffer (as evidenced by the higher SVR and PP/SVI ratio in the elderly subjects) and more resistive vasculature, this resulted in a larger increase in SBP.

We found that left ventricular contractility in the face of an acute afterload increase was preserved in older subjects. All measures that reflected contractility (EF, ESVI, SVI, SWI, and LVCI) were not altered by aging. Our findings conflict with the results of several previous investigations which used different experimental designs. Turner et al.[15] found evidence of a reduced contractile response with aging uncovered during phenylephrine infusion, as determined by the slope of the systolic shortening-end systolic wall stress relationship (an echocardiographic measurement). There were several major differences between our study and this study. The echocardiographic measures used by Turner et al., are somewhat less reproducible than the radionuclide measures used in our study in clinical situations that affect ventricular distensibility such as hypertension and aortic stenosis. In fact an examination of patients with hypertension and aortic stenosis have shown that it is possible to have a normal shortening-end systolic wall stress relationship yet still have a significant reduction in EF during exercise[24]. Since aging is also associated with mild changes in ventricular distensibility[25] this would provide another possible mechanism for the age-associated difference observed by Ehsani et al. In contrast, the reproducibility of the radionuclide angiographic measures used in our study have been shown to be quite good[16]. Additionally, Turner et al gave each subject an identical dose (1.0 mg) of atropine prior to the phenylephrine infusion, despite the fact that the older subjects in the study had a trend towards higher weights than the younger subjects. Therefore the more obese older subjects in Turner's study (who received a smaller relative atropine dose) may have had relatively more parasympathetic tone during the phenylephrine infusion than the thinner younger subjects, who received a higher relative atropine dose. Therefore the difference in contractile response to phenylephrine seen in Turner's study may have been due to the differential relative atropine dose given to each group, rather than an age associated change in the phenylephrine response[15].

The impairment in the baroreceptor-mediated bradycardic response to phenylephrine is consistent with much previous work which shows a reduction in baroreceptor sensitivity with increasing age[26-28]. It has been suggested that phenylephrine exerts a positive chronotropic effect which becomes attenuated with aging[29,30]. Indeed, Turner et al. demonstrated an increase in heart rate with the initial infusion of phenylephrine in the younger as opposed to the older subjects[15]. This phenomenon was not observed in our study as our subjects did not receive atropine as in Turner's investigation; the chronotropic effect seen by Turner et al. was most likely overwhelmed by the vagally-mediated bradycardic response in our subjects.

Limitations

The observed changes in hemodynamics with phenylephrine are due to the infusion itself and also due to secondary reflex mediated changes. Perhaps an underlying impairment in the older subjects' contractile response was masked by an age-associated difference in the baroreflex-mediated vagal tone response. The lack of an effect of age on changes in the phenylephrine response of RMS difference (an indirect marker of vagal tone) suggests that this was not the case, however. Although the validity of heart rate variability has been quite controversial with respect to measuring sympathetic nervous system activity[31-33] recent work by Polanczyk et al.[32] and in our own laboratory[33] have shown that heart rate variability successfully determines vagus activity. Conclusions regarding the effect of age on the phenylephrine response in women cannot be determined. There were not enough female subjects in this study to be able to comment on any gender differences in the effect of phenylephrine. In addition, the methods used in this study are relatively crude measures of contractility when compared with more invasive measures. We did not feel that such invasive measures were justifiable in a healthy, normal sample.

In conclusion, we found no evidence for an age-associated reduction in the contractile response to an acute increase in afterload in a well-screened population of normal older subjects. The SBP response to acute α_1-stimulation is exaggerated in the older population likely as a result of a normal contractile response in the face of a stiff, more resistive vasculature.

Table 2—Mean Responses to Phenylephrine in Young (n=12) and Older (n=15) Adults

	REST	0.5mcg/kg min	1.0 mcg/kg/min	p Value Young/Old	p Value PE effect	p Value Age*PE
HR(b / min)						
Young	66.9±1.4	60.1±1.6	52.5±1.7	0.55	<0.0001*	0.05*
Old	63.7±1.2	59.3±1.0	53.5±1.3			
SBP(mm Hg)						
Young	126±4	132±4	142±4	0.01*	<0.0001*	0.003*
Old	134±3	146±4	163±4			
DBP(mm Hg)						
Young	75±2	84±3	90±4	0.29	<0.0001*	0.87
Old	79±2	87±2	93±2			
MAP(mm Hg)						
Young	91±2	99±3	107±4	0.21	0.009*	0.65
Old	97±2	109±4	108±10			
CI(L/minXm^2)						
Young	2.7±0.2	2.4±0.1	2.2±0.1	0.09	0.003*	0.03*
Old	2.0±0.2	2.1±0.2	1.9±0.2			
EDVI(mL/m^2)						
Young	61.8±3.9	66.0±2.2	70.0±3.5	0.20	0.0001*	0.57
Old	53.4±4.1	61.8±4.1	62.9±4.5			
ESVI(mL/m^2)						
Young	22.1±2.3	26.5±1.7	28.9±2.3	0.70	<0.0001*	0.63
Old	21.3±2.3	26.2±2.4	26.7±2.2			
SVI(mL/m^2)						
Young	39.6±3.0	39.6±1.9	41.0±1.9	0.14	0.08	0.32
Old	32.1±2.7	35.6±2.8	36.3±3.3			
EF(%)						
Young	64.5±2.9	59.9±2.2	59.0±1.7	0.37	<0.0001*	0.31
Old	60.3±2.2	57.8±2.3	57.3±1.9			
SVR(dynes s cm^{-5})						
Young	1462±106	1721±92	2047±120	0.001*	<0.0001*	0.54
Old	2209±159	2298±136	2790±208			

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CI, cardiac index; EDVI, enddiastolic volume index; ESVI, endsystolic volume index; SVI, stroke volume index; EF, ejection fraction; SVR, systemic vascular resistance
* p<0.05 by ANOVA for repeated measures

Table 3—Response to Phenylephrine of Derived Measurements in Young (n=12) and Older (n=15) Adults

	REST	0.5 mcg/kg/min	1.0 mcg/kg/min	p Value Young/Old	p Value PE effect	p Value Age*PE
RMS Diff (ms)						
Young	67.4±4.4	68.6±9.1	82.2±8.4	0.02*	0.0004*	0.62
Old	44.4±4.2	50.3±5.4	68.8±7.0			
E_a (mmHg/mL)						
Young	1.4±0.1	1.5±0.1	1.5±0.1	0.001*	0.13	0.48
Old	2.1±0.2	2.0±0.1	2.2±0.2			
LVCI(mmHg/mLxm^2)						
Young	6.7±1.0	5.2±0.4	5.2±0.4	0.23	0.004*	0.39
Old	7.1±0.7	6.2±0.5	6.6±0.6			
RPP (mmHgxb/min)						
Young	8436±351	7946±332	7457±326	0.20	0.14	0.45
Old	8457±210	8845±313	8135±662			
PP/SVI(mmHgxm^2/mL)						
Young	1.4±0.1	1.3±0.1	1.3±0.1	0.005*	0.09	0.06
Old	1.8±0.1	1.7±0.1	2.1±0.2			
SWI(mLxmmHg/m^2)						
Young	5008±425	5205±278	5860±362	0.75	<0.0001*	0.07
Old	4308±395	5235±499	5938±618			

RMS Diff, root mean square difference of successive RR-intervals; E_a, vascular load; LVCI, left ventricular contractility index; RPP, rate pressure product; PP/SVI, pulse pressure/stroke volume index; SWI, stoke work index
* p<0.05 by ANOVA for repeated measures

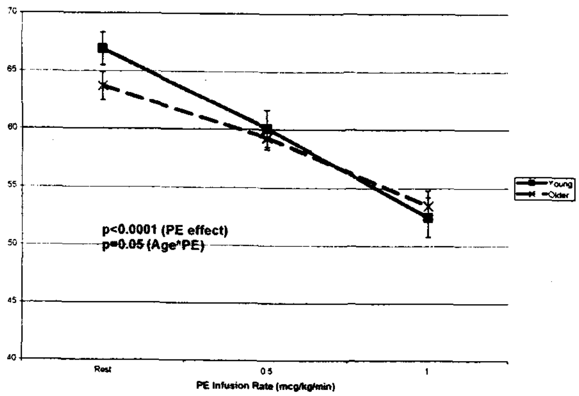

Figure #1: Effect of Phenylephrine on Heart Rate
Change in heart rate (beats/min) during 0.5 and 1.0 mcg/kg/min phenylephrine (PE) infusion in both young (n=12) and older (n-15) subjects. Older subjects had a significantly lower heart rate decrease in response to PE than the younger subjects.

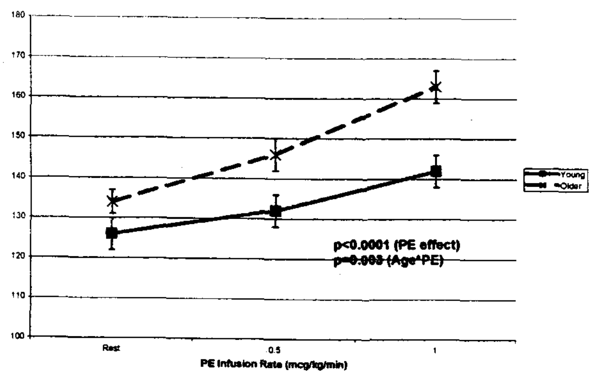

Figure #2: Effect of Phenylephrine on Systolic Blood Pressure
Change in systolic blood pressure (SBP, mm Hg) during 0.5 and 1.0 mcg/kg/min phenylephrine (PE) infusion in both young (n=12) and older (n=15) subjects. Older subjects had a significantly larger SBP respose to PE infusion.

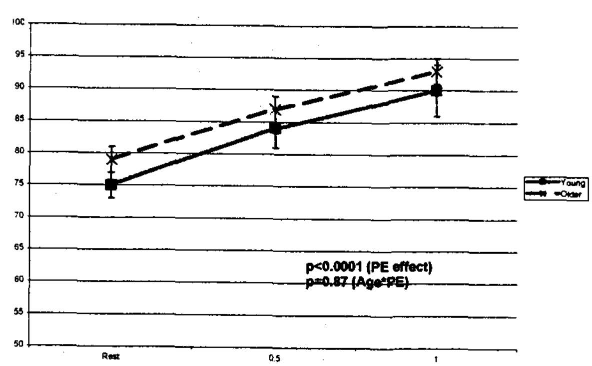

Figure # 3: Effect of Phenylephrine on Diastolic Blood Pressure
Change in diastolic blood pressure (DBP, mm Hg) during 0.5 and 1.0 mcg/kg/min phenylephrine (PE) infusion in both young (n=12) and older (n=15) subjects. There was no age-associated change in the DBP response to PE.

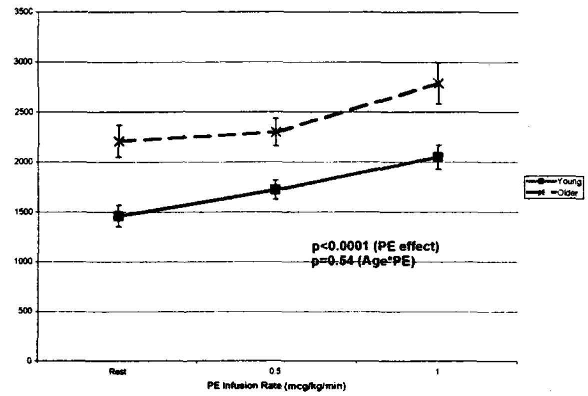

Figure #4: Effect of Phenylephrine on Systemic Vascular Resistance
Change in systemic vascular resistance (SVR, dynes s cm-5) during 0.5 and 1.0 mcg/kg/min phenylephrine infusion in both young (n=12) and older (n=15) subjects. SVR was higher in older subjects at rest and at each infusion rate. There was no age-associated change in the SVR response to PE, however.

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